Addressing the complexity of prenatal and postnatal environmental exposures affecting childhood lung function

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See Articles page e79

Environmental pollution affects morbidity and mortality in children aged 0–5 years, not only in developed countries, but also in low-income and middle-income countries in particular.[1] However, environmental exposures during this period of increased susceptibility in infants and children might have long-lasting effects that are often underestimated. Air pollution exposure during pregnancy is associated with reduced postnatal lung function,[2] and several studies also show a sustained effect of prenatal air pollution exposure on lung function at age 5 weeks up to age 11 years.[3] Low lung function in early childhood can persist into adulthood, and is often associated with persistent respiratory morbidity and even chronic obstructive pulmonary disease in later life.[4] Impaired lung functional development might therefore be an important link between the detrimental effects of environmental factors in pregnancy and early infancy, and long-term respiratory morbidity. The effect of these pollutants on lung function growth trajectories is, however, highly complex. The timing of susceptibility during lung tissue development might vary for different pollutants.[5] Mechanisms of action are manifold[6] and involve toxicity, endocrine dysfunction, impaired development, and epigenetics. Exposures of several environmental pollutants are collinear, and whether these stressors act independently or synergistically with potential cumulative effects is unclear. Most pollutants have small effect sizes; however, little is known with respect to timing of the exposure and dose–response effects. It is unclear whether thresholds exist below which the exposure can be deemed safe, and whether such effect thresholds depend of the age of the child. Preliminary evidence from our research group[7] shows that exposure to low doses of air pollutants (ie, nitrogen dioxide) in the first 2 years of life was associated with reduced lung function at a mean age of 6 years, despite these exposure levels being below the recommended WHO threshold levels for adults.[7]

With regard to understanding the complexity and the variety of detrimental effects of environmental factors on lung development,[8] Agier and colleagues[9] make a substantial contribution with their study published in *The Lancet Planetary Health*. The authors chose an observer-independent environment-wide association study (EWAS) approach and investigated the effects of a large set of exposures. This so-called exposome[10] allowed for a comprehensive assessment of lung development and might help to determine the dominant environmental risks. The authors prospectively investigated the association of this exposome (210 prenatal and postnatal environmental stressors) on spirometry outcomes in children aged 6–12 years within six population-based European birth cohorts. High-quality spirometry measurements were assessed in 1033 children. They found that two prenatal exposures (perfluorononanoate and perfluorooctanoate) were associated with lower forced expiratory volume in 1 s percent predicted values (FEV_1%), whereas inverse distance to nearest road during pregnancy was associated with higher FEV_1%. Nine postnatal exposures (copper, ethyl-paraben, five phthalate metabolites, house crowding, and facility density around the school) were associated with lower FEV_1%.

The authors used sophisticated statistical models to select the most relevant exposures and properly adjusted for multiple comparison errors. The authors report that no exposure passed the significance threshold after adjustment for multiple testing, indicating that a single exposure might only have a very small effect. Although this dataset is the largest available, the sample size is still relatively small, which means that the sensitivity for pollutants with small effect sizes would have been low. These minor effects might be better detected by targeted approaches investigating specific exposures.[3] Nevertheless, the authors have, so far, detected unrecognised, dominant environmental pollutants and quantified their relative importance with respect to well-known exposures.

This novel approach, however, like most environmental exposure studies, might carry a risk with respect to reverse causation errors. Additionally, the sample size and study design limit the ability to detect interactions between exposures or cumulative effects. Small size effect sizes or interactions might be better detected in future studies with substantially larger sample sizes. Sample size aside, validating the associations in replication cohorts while accounting

for known physiological clinical adjustments would enhance the validity of any environmental exposure outcome study.

EWAS is an important new method for better understanding the effects of environmental factors on lung function growth. This primarily hypothesis-generating approach needs to be carefully combined with targeted birth cohort studies, prevention studies, and, in particular, longitudinal studies. For example, studies could measure lung function at birth and exposures in pregnancy, followed by lung function at age 6–12 years and exposure measurements at age 0–3 years, and then even continue into adulthood. Characterising such lung function growth trajectories in relation to the progression of respiratory disease would enable a better understanding of the mechanisms involved. Furthermore, animal and cell models might be needed to understand the mechanism of action of toxic substances detected by these EWAS analyses. Research into which infants are exposed to particular environmental substances is needed to better target preventive measures.

Exposome studies reveal novel, undetected environmental pollutants and relevant determinants of lung function development. Impaired lung function growth is associated with subsequent long-term respiratory morbidity in adulthood, but we cannot yet estimate the full impact of today's pollution on health and health economics over the next 50 years. This issue is particularly relevant in low-income and middle-income countries,[1] where implementation of effective preventive measures is even lower.

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